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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/665,111	09/16/2003	Dolores Schendel	1406/468	6128

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1643	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/665,111	SCHENDEL ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-30 and 32-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-30, 32-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

After review and reconsideration, the finality of the Office action of June 11, 2008 is withdrawn. The amendment filed October 21, 2008 has been entered. Claims 23, 27 and 33 have been amended. Claims 23-30, 32-46 are pending and under consideration.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23-30, 32-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 23, 27, 28, 33 and 38 are vague and indefinite in the recitation of "proteins and/or peptides or RNA or DNA or cDNA encoding said proteins and/or peptide which are over expressed in tumor cells". It is unclear if the first occurrence of "proteins and/or peptides"' is to be subject to the qualifier of "over expressed in tumor cells" or if the "peptides which are over expressed in tumor cells" is a separate species. For purpose of examination, all alternatives will be considered.

Claims 29 and 41 are vague and indefinite in the recitation of "proteins and/or peptides or RNA or DNA or cDNA encoding said proteins and/or peptides from several different tumor cell lines". It is unclear if "peptides from several different tumor cell lines is to be applied as a separate species or to limit the cDNA encoding, or if that limitation is to be applied to all the recited species. For purpose of examination, all alternatives will be considered.

Claim 24 is vague and indefinite because it is unclear if the modifier of "peptides from several different tumor cell lines" is a separate species, or limits the cDNA encoding or the entirety of the recited species.

Claim 41 is vague and indefinite in the recitation of "introduced for the treatment of tumor diseases in said patient". The claim lacks an explanation of how the cells are "introduced", such as "introduced to the public" by an advertisement or "administered to

the patient". Further, it is unclear how the intended use of the cells further limits the scope of claim 41.

Claim 42 is vague and indefinite because it fails to provide an object into which the cell lines are introduced.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 23, 24, 27, 28, 29, 30, 32, 33, 34, 37, 40, 41, 43 and 44 are rejected under 35 U.S.C. 102(e) as being anticipated by Vachula et al (U.S. 6,458,585).

Claims 23 and 24 are drawn in part to a method for the generation of HLA-haploidentical antigen-presenting cells for the treatment of tumor diseases in a patient comprising the following steps of providing antigen-presenting cells from a semi-allogeneic donor which are HLA-haploidentical with respect to those of the patient; and introducing proteins or peptides. Claim 40 embodies the method of claim 23 wherein the APC are dendritic cells. Claim 40 requires that the antigen-presenting cells are dendritic cells or macrophages. Claim 41 specifies that the antigen presenting cells have been introduced form the treatment of tumor diseases in said patient.

Claims 27-29 are drawn in part to a composition comprising antigen presenting cells into which proteins and/or peptide which are introduced, wherein the APC are semi-allogeneic and HLA haploidentical with respect to those of the patient. Claim 28 specified that the proteins and or peptides which are introduced are selected from a group including carcinomas and cells of ectodermal tumors. Claim 30 requires that the antigen-presenting cells are dendritic cells or macrophages. Claim 32 specifies that the

composition of claim 27 is a vaccine. Claim 43 embodies the composition of claim 28 wherein the ectodermal tumor is melanoma.

Claim 33 is drawn in part to a method comprising administering to a patient a therapeutically effective amount of semi-allogeneic HLA-haploidentical antigen presenting cells into which proteins and or peptides have been introduced. Claim 34 specified that the cells are used for the treatment of tumors comprising re selected from a group including carcinomas and cells of ectodermal tumors. Claim 37 embodies the method of claim 33 wherein the cells are applies by the intravenous route. Claim 44 embodies the method of claim 34 wherein the ectodermal tumor is melanoma.

Vachula et al disclose a method of making loaded dendritic cells by pulsing with antigen (column 8, lines 27-35). Vachula et al disclose that the antigens can be used to produced antigen-specific dendritic cells for treatments against various carcinomas and melanoma (column 8, line 63 to column 9, line 8). Vachula et al disclose that the antigen pulsed dendritic cells can be washed, concentrated and infused directly into a patient as a type of vaccine against tumor cells (column 9, lines 14-16) via a intravenous infusion (column 6, lines 56-58). Vachula et al disclose that ideally the donor and recipient will be completely HLA matched, which can occur fortuitously among full siblings (column 5, lines 19-21), thus fulfilling the specific embodiment of semi-allogeneic with respect to "siblings" and haploidentical with respect to "completely HLA-matched".

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under

37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 23, 24, 26-30, 32-35, 37, 40, 41, 43 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vachula et al (U.S. 6,458,585)

Claims 26 and 35 embody the methods of claim 23 and claim 35 respectively, wherein the APC from two different HLA-haploidentical individuals are used.

Vachula et al teach the preferred embodiment of having a completely HLA-matched dendritic cell donor such as a sibling. Vachula et al do not specifically teach using two completely HLA-matched dendritic cell donors.

It would have been prima facie obvious at the time that the claimed invention was made to use two different completely HLA-matched donors such as two offspring, in the event that the donors were unable to provide sufficient starting mononuclear cells, or said mononuclear cells did not undergo sufficient expansion to provide a therapeutic amount to said patient.

Claims 23-30, 32-41 and 43-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vachula et al (U.S. 6,458,585) as applied to claims 23, 24, 26, 27, 28, 29, 30, 32, 33, 34, 35, 37, 40, 41, 43 and 44 above, and in further view of Nair et al (U.S. 5,853, 719, cited in a previous action).

Claims 25 and 36 embody the methods of claim 23 and claim 36, respectively wherein RNA from tumor cells is reverse transcribed into cDNA following by cDNA amplification by means of PCR. Claim 38 embodies the method of claim 23 wherein the proteins or peptides have been introduced in recombinant form. Claim 39 embodies the method of claim 23 wherein RNA or DNA or cDNA is introduced into the haploidentical APC, wherein the cDNA encodes tumor defined antigens which are over expressed in the tumor cells. Claim 45 embodies the method of claim 39 wherein the tumor defined antigens are selected from the group including proteins providing a growth advantage to

the tumor and/or ensuring its survival. Claim 46 embodies the method of claim 45 wherein the tumor antigens are Her-2/neu, PSMA, WT-1, MUC-1 or telomerase.

Vachula et al teaches that protein or peptide antigens can be Her-2/neu or MUC-18, line 63 to column 9, line 3), thus fulfilling the limitations of claims 45 and 46. Vachula et al does not specifically address the use of cDNA reverse transcribed and amplified from RNA as a recombinant source of the peptides or proteins .

Nair et al teach method for the loading of dendritic cells by introduction of a tumor associated RNA which is unfractionated or cDNA made by PCR (page 3, lines 13-19). Nair et al disclose that the method offers advantages in that there is no need to identify specific tumor rejection antigens and an immune response to unfractionated RNA or cDNA made therefrom elicits immune responses to several tumor antigens reducing the likelihood of escape mutants and extends the use of active immunotherapy to the treatment of cancers for which specific tumor antigens have not yet been identified which is the vast majority of cancers (page 9, lines 21-35). Nair et al teach a method for treating cancer comprising directly administering the loaded dendritic cells to a patient suffering from cancer (claims 51-53).

It would have been prima facie obvious at the time the claimed invention was made to substitute the RNA or cDNA transfection for peptide pulsing in the method of administering dendritic cells to a patient having cancer as taught by Vachula et al. One of skill in the art would have been motivated to do so by the teachings of Nair et l regarding the improvements associated with using unfractionated RNA for the loading of dendritic cells, and the administration the loaded dendritic cells as part of the immunotherapy as taught by Nair et al.

Claims 23-30 and 32-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vachula et al (U.S. 6,458,585) and Nair et al (U.S. 5,853, 719) as applied to claims 23-30, 32-41 and 43-45 above, and further in view of Storkus et al (U.S. 6,077,519, cited in a previous Office action) and Warnier et al (WO 98/58956, cited in a previous action).

Claims 24 and 41 embody the method of claim 23 wherein proteins, peptide, RNA, DNA or cDNA from several different tumor cell lines are introduced into the HLA-haploidentical APC. Claim 29 embodies the composition of claim 27 wherein the APC contain cDNA encoding proteins and/or peptides from several different tumor cell lines. Claim 42 embodies the method of claim 41 wherein pooled cDNA from two or three different tumor cell lines is introduced.

The combination of Vachula et al and Nair et al render obvious the use of cDNA transfection of dendritic cells versus peptide pulsing. The combination does not teach the use of cDNA obtained from several different tumor cell lines.

Storkus et al teach that dendritic cells can be pulsed with HLA-matched allogeneic tumor cell lines as an alternative to acid eluted peptides from the patients tumor cells (column 12, lines 21-32). Storkus et al teach the administration of pulsed dendritic cells by intravenous routes (column 35, lines 53-60). Storkus et al teach that the invention be applied to treat colon, squamous, gastric, breast, prostate, lung, cervical and ovarian carcinomas. It is noted that prostate carcinomas would inherently express prostate specific membrane antigen and thus met the limitation of claim 46.

Nair et al teach that vaccination with dendritic cells loaded with unfractionated tumor-derived RNA likely elicits immune responses to several tumor antigens thus reducing the likelihood of "escape mutants" (column 4, lines 3-5).

Warnier et al teach that tumors express a set of tumor antigens, of which only certain subsets may be expressed in the tumor of any given patient and the desirability of having antigen-presenting cells expressing "polytopes" comprising multiple epitopes on tumor antigens in order to reflect a boarder spectrum of tumor associated antigens (page 20, line 31 to page 21, line 7)

It would have been prima facie obvious at the time the claimed invention was made to use pooled tumor cell acid eluted peptides or RNA or cDNA for pulsing or loading the dendritic cells used in the methods rendered obvious by the combination of Vachula et al and Nair et al. One of skill in the art would have been motivated to do so by the suggestion of Storkus et al that cell lines can be used as a source of tumor specific antigen peptides. One of skill in the art would have been motivated to look to this source

in the event that no tumor material from the patient was available or insufficient. One of skill in the art would have been motivated to used pooled acid eluted peptides or unfractionated RNA or unfractionated cDNA from several different tumor cell lines because of the teachings of Nair et al regard tumor escape mechanisms. One of skill in the art would understand that providing a multitude of antigens to the dendritic cell would compensate for the ability of a tumor to down regulate an antigen and escape immune surveillance and the teachings of Warnier et al on the restricted expression of antigen on patient tumors. One of skill in the art would have been motivated to include the antigens from several different tumor cell lines in order to insure that the antigen presenting cell would provide antigens which were expressed on the actual patient tumor. One of skill in the art would understand that the more tumor specific antigens which can be expressed by the activated dendritic cells, the more populations of activated T cells will be available for recognition of tumor cells. Further, because the method is taught by Storkus et al to extend to the treatment of prostate cancer, the unfractionated RNA, cDNA made therefrom would inherently include prostate specific membrane antigen, PSMA, thus fulfilling the limitations of claims 45 and 46.

All other rejections and objections as set forth or maintained in the previous Office action are withdrawn.

All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A Canella/
Primary Examiner, Art Unit 1643